PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 April 2000 (12.04.00)	
International application No. PCT/CH99/00384	**Applicant's or agent's file reference** SMGD
International filing date (day/month/year) 19 August 1999 (19.08.99)	**Priority date** (day/month/year) 21 August 1998 (21.08.98)
Applicant FREY, Felix et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   14 March 2000 (14.03.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FREY, F.
University of Berne
Department of Internal Medicine
Division of Nephrology
Freiburgstrasse
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SUISSE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.12.2000
Applicant's or agent's file reference: SMGD	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CH99/00384	19/08/1999	21/08/1998

Applicant
FREY, Felix et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

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Cardenas, C

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PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	04.09.2000
Applicant's or agent's file reference: SMGD	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CH99/00384	19/08/1999	21/08/1998

International Patent Classification (IPC) or both national classification and IPC

C07J43/00

Applicant

FREY, Felix et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 21/12/2000.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
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Authorized officer / Examiner

Watchorn, P

Formalities officer (incl. extension of time limits)
Cardenas, C
Telephone No. +31 70 340 3370

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-68 as originally filed

Claims, No.:

1-29 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-13,17-29 (not searched in part) 14-16 (not searched at all),

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-13,17-27 (searched in part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-13,17-29 (searched in part) 14-16 (not searched at all).

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-13,17-29 (in part).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	25
Inventive step (IS)	Claims	1-13,17-29
Industrial applicability (IA)	Claims	23,24,26,28

2. Citations and explanations

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III - Non-Establishment of an Opinion

1) The compounds of claims 1-16 are defined in terms of a result to be achieved, i.e. in terms of being a conjugate between a "steroid hormone" and a "DNA interacting molecule". These two terms do not have a well established meaning in the art and do not provide the skilled person with sufficient information to determine firstly the true scope of these claims, and secondly whether or not the claim is indeed differentiated over the prior art. The true nature of the subject matter of these claims is such that it is so vague, obscure and unclear according to Art. 6 PCT that a meaningful search could not be carried out on these claims in full. Consequently the search was limited to those specific groups of "steroid hormones" and "DNA interacting molecules" that the applicant mentioned and sufficiently defined and exemplified in the application as provided for under Article 17(2)(a)(ii),(b) PCT. The above applies equally to the compositions, synthesis and uses of these compounds specified in claims 17-29. Furthermore, the terms "incorporating molecules" used to further define the DNA interacting molecule in claim 13 is so unclear, and is further not elaborated in the description by means of any examples, that it is as unclear as the more generic term ("DNA interacting molecule") of which it is a preferred value. Consequently this term was not taken into consideration in drafting the present non-unity since it is so obscure within the meaning of Art. 6 PCT and is consequently also excluded from any search under Art.17(2)(a)(ii)(b) PCT. Exactly the same applies to the term "Synthetic steroids" as used in claim 12.

2) Consequently the same subject matter of the present application as was excluded from the international search is now also excluded from examination according to Art.34(4)(a)(ii) PCT and for the same reasons (given above) of a lack of clarity that lead to the partial search. The examination is limited to that subject matter which was subject to an international search, additionally because the International Preliminary Examining Authority is under no obligation to examine unsearched subject matter (Rule 66.1(e) PCT).

Section IV - Lack of Unity of Invention

The most relevant prior art with regard to the unity of the present application consists of the following documents:-

D1 = WO-A-96/18372
D2 = WO-A-96/03875
D3 = WO-A-94/23751
D4 = WO-A-93/07283

The presently claimed subject matter relates to conjugates of steroid hormones with chemical groups which bind to nucleic acids (in particular DNA). The problem to be solved by the subject matter of this application (i.e. by these compounds) is the provision of agents capable of transfecting nucleic acids into the cell nucleus (see page 4, paragraph 1 of the description). It is this combination of the nuclear specificity conferred by the steroid hormone and the nucleic acid (NA) binding capability of the NA-interacting group present in the claimed compounds which is common to the claimed subject matter as a whole (which claims either the compounds per se, their uses compositions and syntheses) and which may serve to unify the claimed subject matter a priori.

In this regard it is noted that the above documents all disclose compounds which consist of conjugates of steroid hormones with chemical groups which interact with nucleic acids, see in particular:-

D1 - page 26, lines 1-21 and page 27 lines 8-18 and page 30, lines 6-10.

D2 - page 11, example 1

D3 - fig 1, page 34, example 1.10

D4 - page 46, paragraph 2 - page 47, paragraph 1

In the above mentioned passages document D1 discloses the conjugation of androsterone, other sex steroids and Vitamin D derivatives and corticoid steroids to a cationic group, D2 discloses the conjugation of dihydrotestosterone to a polylysine group, document D3 discloses the conjugation of estradiol to a polycationic peptide and document D3 discloses the general concept of conjugating an "internalisation factor" with a DNA binding agent, in particular, D4 mentions on page 46, paragraph 2- page 47, paragraph 1, the use of thyroid hormone (the applicant intends the term "steroid hormone" as used in claim 1 to include thyroid hormone - see claim 10) as the "internalisation factor" and, for example, polycations such as polylysine as the DNA binding agent (see page 49, paragraphs 2,3 of D4) or intercalating agents such as acridine or ethidium (see page 49, paragraph 4 - page 50 paragraph 1 of D4).

Furthermore, the steroid-DNA binding group conjugates of all of the above documents are directed to the solution of the same problem (delivery of nucleic acids to the cell nucleus) - see D1, page 21, paragraph 2, D2, page 12, paragraph 3, D3, page 4, paragraph 2 and D4 page 8, paragraph 2). Consequently documents D1-D4 represent the same technical solution to the same technical problem. Consequently the above mentioned feature, common to the claimed subject matter as a whole, has already been associated with the solution to the same problem in the prior art. Consequently this technical feature of the claimed subject matter cannot be considered to be the common or corresponding special technical feature within the meaning of Rule 13.2 PCT which differentiates the claimed subject matter as a whole over the prior art. Since according to Rule 13.2 PCT the presence of such a common or corresponding special technical feature is an absolute prerequisite for unity to be established, and given that there does not appear to be any other technical feature common to the claimed subject matter as a whole which might be able to fulfill this role, the currently claimed subject matter lacks unity according to Rule 13.1 PCT.

Consequently the claimed subject matter was firstly broken up on the basis of the nature of the steroidal part of structure (subject to the restrictions made under Rule 66.1(e) PCT and Article 34(4)(a)(ii) PCT see Section III above). This division of the claimed subject matter establishes a further essential feature (which in the present case is the nature of the steroid group, estrogen, androgen... etc) which was originally presented in the claims as one of a number of alternatives, but is made an essential feature of each of the subjects of the present non unity, such that each of the subjects

into which the presently claimed subject matter has been split, presents one further common technical feature (i.e. essential feature) which is a candidate to be a common or corresponding special technical feature. This division of the claimed subject matter results in 7 claimed inventions being conjugates of DNA interacting molecules with respectively:-

(1) corticoid hormones (embracing mineral and gluco-corticoids),

(2) androgens,

(3) estrogens,

(4) gestagens (progesterone agonists)

(5) * retinoids

(6) * thyroid hormones and

(7) * vitamin D derivatives

*(NOTE, according to the applicant's definition the term "steroid hormone" embraces retinoids, thyroid hormones and vitamin D compounds - see page 5, last paragraph).

However, as has already been shown above cited documents conjugates of NA interacting groups with various steroid hormones have already been disclosed as solutions to the same problem in the prior art, these hormones of the conjugates being specifically:-

(a) androgens (see D1, page 27, lines 8-18 where androsterone is conjugated to polyamine-NA interacting groups, see D2 page 11, and example 1, where dihydrotestosterone is conjugated to NA-interacting polylysine)

(b) estrogens (see D3, Fig 1, and page 34, example 1.10 where estradiol is conjugated to a cationic DNA interacting peptide)

(c) corticoid compounds (see D1, page 26, lines 1-21 where the conjugation of corticoid compounds to NA interacting polyamines is disclosed)

(d) Vitamin D derivatives (see D1, page 26, lines 1-21 where the conjugation of Vitamin D compounds to NA interacting polyamines is disclosed).

(e) sex hormones in general (see D1, page 26, lines 1-21 where sex hormones in general, which includes the well known class of progesterone agonists, including progesterone itself, which is also disclosed for this use in claim 3 of D3)

(f) thyroid hormones (see D4, page 46, paragraph 2 - page 47, paragraph 1)

Consequently the additional common technical feature of above subjects (1)-(4), (6) and (7), which may have unified these claimed inventions a priori, has also already been associated with the solution to the same technical problem in the prior art. Consequently in the case of above identified subjects (1)-(4) (6) and (7), the nature of the "steroid hormone" part of the molecule cannot be considered to be the common or corresponding special technical feature within the meaning of Rule 13.2 PCT which distinguishes the subject matter of each of these claimed inventions as a whole over the prior art. Since no other technical feature could be identified in any of these subjects which might be able to fulfill this role, and further given that according to Rule 13.2 PCT the presence of such a special technical feature is an absolute prerequisite for unity to be established, these claimed inventions further lack unity within themselves according to Rule 13.1 PCT. Consequently yet another technical feature, originally presented in the application as originally filed as an alternative feature, is taken into consideration in further dividing up the claimed subject matter of these claimed inventions. This feature is the nature of the NA-interacting group (intercalator, cross

linking agent... etc).

Consequently each of claimed inventions (1)-(4) (6) and (7) as identified above, has been further split on the basis of the NA-interacting group (subject to the restrictions mentioned in section III above), such that it present yet another essential feature which acts as a further candidate for the special technical feature within the meaning of Rule 13.2 PCT.

With due regard to the decision T110/82 concerning the relationship between the interests of a rational procedure up to grant, in which interconnected matter should not needlessly be split up nor unrelated inventions lumped together for the purposes of saving fees, in particular since the expense for the procedure for such cases must be partly borne by the fees levied for other applications, the present application has been split up as follows, based on the different characterising features of these claimed inventions as set out below, and pursuant to Article 34(3)(a) PCT.

1. Claims: 1-13,17-29 (in part)
Conjugates of corticoids with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

2. Claims: 1-14, 17-29 (in part) 15,16 (in full)
Conjugates of corticoids with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

3. Claims: 1-13,17-29 (in part)
Conjugates of corticoids with DNA-ionic-interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

4. Claims: 1-9,12,13,17-29 (in part)
Conjugates of androgens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use

in cell transfection, cells transfected therewith and assays for that transfection.

5. Claims: 1-9,12-14,17-29 (in part)
Conjugates of androgens with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

6. Claims: 1-9,12,13,17-29 (in part)
Conjugates of androgens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

7. Claims: 1-9,12,13,17-29 (in part)
Conjugates of estrogens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

8. Claims: 1-9,12-14,17-29 (in part)
Conjugates of estrogens with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

9. Claims: 1-9,12,13,17-29 (in part)
Conjugates of estrogens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

10. Claims: 1-9,12,13,17-29 (in part)
Conjugates of gestagens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

11. Claims: 1-9,12-14,17-29 (in part)

Conjugates of gestagens with DNA-cross linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

12. Claims: 1-9,12,13,17-29 (in part)
Conjugates of gestagens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

13. Claims: 1-9,12-14,17-29 (in part)
Conjugates of retinoids with DNA-intercalating agents, cross linking agents or ionic interacting agents methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

14. Claims: 1-9,12,13,17-29 (in part)
Conjugates of Vitamin D compounds with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

15. Claims: 1-9,12-14,17-29 (in part)
Conjugates of Vitamin D compounds with DNA-cross linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

16. Claims: 1-9,12,13,17-29 (in part)
Conjugates of Vitamin D compounds with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

17. Claims: 1-9,12,13,17-29 (in part)

Conjugates of thyroid hormones with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

18. Claims: 1-9,12-14,17-29 (in part)
Conjugates of thyroid hormones with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

19. Claims: 1-9,12,13,17-29 (in part)
Conjugates of thyroid hormones with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

However, since the same finding of a lack of unity as made above was also raised at the stage of the international search (involving the division of the claimed invention into the same 19 different separate claimed inventions) and the applicant did not pay any additional search fees for any of the additional 18 claimed inventions according to Art.17(3)(a) PCT, Rule 40.2(a) PCT and the then valid Rule 104a(1) EPC (as of 01.03.2000 renumbered to Rule 105(1) EPC), only the main invention first mentioned in the claims (claimed invention 1 - see above) was subject to an international search according to Art.17(3)(a) PCT and no search was carried out in respect of any of claimed inventions 2-18. Consequently, since the EPO acting in its capacity as International Preliminary Examining Authority is not obliged to examine unsearched inventions (Rule 66.1(e) PCT) no invitation to pay additional examination fees has been sent according to Art.34(3)(a) PCT, Rule 68.2 PCT and Rule 105(2) EPC.

Section V - Assessment of Novelty, Inventive Step and Industrial Applicability

The following documents constitute the most relevant state of the art:-

D1 = WO-A-96/18372
D5 = Bioorg. Med. Chem. Lett. Vol 5(15) pp 1577-1580 (1995)
D6 = Chem. Abs. Vol 125:058,963

The following documents are also relevant for the assessment of the patentability of the claimed invention:-

D7 = Bioconjugate Chem. Vol 4(1) pp 85-93 (1993)
D8 = Bioconjugate Chem. Vol 2(4) pp 226-231 (1991)

Industrial Applicability (Art.34(4) PCT)

1) For the assessment of the present claims 23,24,26 and 28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty (Art.34(2) PCT)

1) The conjugates of glucocorticoids and DNA-intercalating agents of above identified claimed invention 1 and claimed per se in claims 1-13 differentiate themselves over the cation-corticoid conjugates of D1 - see page 26, lines 1-21 in that they the DNA-binding component of the conjugate is DNA-intercalating group whereas that of the conjugate of D1 is a cationic DNA-binding agent, which binds DNA by ionic interaction with the negatively charged phosphate backbone. The claimed conjugates are novel over the conjugates of documents D5 and D6 (D5 - see the figure on page 1578 and page 1577, paragraph 1; ,D6 - see the abstract), because the conjugates of these documents consist of glucocorticoids conjugated directly to nucleic acids, rather

than being bound to nucleic acid by conjugation to a DNA-interacting group. Consequently the glucocorticoid-DNA-intercalating agent conjugates of claims 1-13 are novel according to Art.34(2) PCT. Since the processes of claims 17-19 are characterised by the production of these glucocorticoid-DNA-intercalating agent conjugates, the subject matter of these claims (in far as they correspond to the production of compounds of claimed invention 1) are also novel according to Art.33(2) PCT. Furthermore, since the complexes of claim 20, the method for their production according to claims 21 and 22, the methods for the use thereof according to claims 23, 24 and 28, the pharmaceutical compositions of claim 27, and an assay for the effectiveness thereof according to claim 29 are all characterised by the use/presence/production of compounds according to claim 1, then these claims are also novel according to Art.33(2) in as far as they relate to uses/methods/complexes/assays characterised by the use/presence/production of glucocorticoid-DNA-intercalating agent conjugates according to claimed invention 1.

2) However, claim 25 relates to a cell transfected with a complex according to claim 20 (consisting of a nucleic acid and a compound according to claim 1). In this regard it is not evident that the use of this particular transfection agent would result in a transformed cell any different from a transformed cell produced by using the same gene transfected by means of a different transfection agent. For example, the transfection experiments disclosed in documents D2 (see example 3), D7 (see page 88, column 2, paragraph 4 - page 89, column 1, paragraph 1), D8 (see page 228, column 1, paragraph 2 - page 229, column 1, paragraph 2) also result in transformed cells containing a newly introduced gene, albeit by means of a different transfection agent to that used to create the cells of claim 25. However, there is no indication in the application nor any technical reason to suppose that the use of the claimed transfection agents (of claimed invention 1) would result in a cell different from one transfected with the same gene, but using a different transfection agent - a product is not necessarily rendered novel by virtue of being produced by a novel process and there is no reason to assume that the use of a different transfection agent would somehow alter the cell produced (improved efficiency of transfection does not mean that the cell is different) - see Preliminary Examination Guidelines IV 7.5. Furthermore, it cannot be argued that the nuclear specificity conveyed on the complex by the presence of the Glucocorticoid in the conjugate could result in a cell transfected in a such a way as to be different over the transfected cells of the state of the art, because the transfection experiment

performed in document D2 made use of steroid-polylysine conjugate which also had nuclear specificity (see page 12, paragraph 3 of D2). Consequently claim 25 lacks novelty over, amongst others, documents D2, D7 and D8 according to Art.33(2) PCT (it would be impossible to cite all documents relating to transfected cells, all of which could potentially prejudice the novelty of claim 25, so the cited documents used in this objection have been limited to those relating to the use of conjugates containing steroid or intercalating groups).

3) The method of claim 26 discloses the use of the transfected cells of claim 25 for the treatment of a human being, whereas documents D1-D4 all disclose the use of the transfection complexes directly in treatment (without first transfecting a cell line and then using this in the treatment). Claim 26 is consequently novel over the above cited prior art according to Art.33(2) PCT.

Inventive Step - Art.33(3) PCT

1) The presently claimed subject matter of claimed invention 1 relates to compounds which are conjugates of corticosteroid hormones with chemical groups which intercalate with nucleic acids (in particular DNA). The problem to be solved by the subject matter of this claimed invention (i.e. by these compounds) is the provision of agents capable of transfecting nucleic acids into the cell nucleus (see page 4, paragraph 1 of the description). The presence of the corticosteroid hormone in the transfection conjugates of claimed invention 1 as claimed *per se* in claims 1-13 confers nuclear specificity on the transfection conjugate and facilitates delivery of the nucleic acid (bound to the intercalating agent part of the conjugate) to the nucleus of the target cell. In this regard it is noted that document D1 clearly indicates the use of corticosteroid hormones attached to nucleic acid binding cationic groups (see page 26, lines 1-21 of D1), where the presence of the corticosteroid hormone confers nuclear specificity on the conjugate and the nucleic acid with which it is complexed (see page 21, paragraph 2 of D1). Furthermore, it is noted that the conjugation of the known glucocorticoid compound - dexamethasone, via a linker group directly to nucleic acids confers nuclear specificity on the nucleic acid (see D5, the figure on page 1578 and page 1577, paragraph 1), D6 indicates the same to be true for the conjugation of deoxycorticosterone to nucleic acids. Furthermore, it is also noted that documents D7 and D8 clearly disclose the use of intercalating agents as a nucleic acid binding group,

conjugated to agents which confer some kind of specificity on the DNA linked to the intercalator component of the conjugate - in D7 this is a conjugate of acridine (intercalator) linked to a cell specific glycoside (see page 86, Figure 1 of D8) which was used successfully in transfection experiments (see page 88, column 2, paragraph 4 - page 89, column 1, paragraph 1 of D7) - in D8 this was ethidium (intercalator) conjugated to transferrin (see page 227, column 2, paragraph 2 - page 228, column 1, paragraph 1 of D8), where the transferrin component of the conjugate facilitated transferring receptor mediated endocytosis of the [transferrin-ethidium]:DNA complex into the target cell. The skilled person, when confronted by the above mentioned problem, would transfer the above teaching of documents D7 and D8 (that the DNA-binding group of a [DNA-binding-group]-[specificity-conferring-group] - transfection agent, can be a nucleic acid intercalating agent such as acridine or ethidium) over to the above mentioned teaching of D1, D5 and D6 (that the presence of a glucocorticoid as the specificity conferring group in such a [DNA-binding-group]-[specificity-conferring-group] - transfection agent confers nuclear specificity of nucleic acid delivery). This obvious step results in the [glucocorticoid]-[intercalating agent] conjugates of claimed invention 1 as claimed *per se* in claims 1-13, consequently these compounds are an obvious solution to the above mentioned problem and as such lack inventive step according to Article 33(3) PCT, since the uses/processes/methods/complexes of claims 17-29 do not appear to possess and further technical features which might render these claims inventive in their own right, they also lack inventive step according to Article 33(3) PCT.

Section VII

1) The applicant has not ackowledged documents D1-D3 as the closest state of the art in the description as required by Rule 5.1(a)(ii) PCT.

Section VIII

1) The compounds of claims 1-13 are defined in terms of a result to be achieved, i.e. in terms of being a conjugate between a "steroid hormone" and a "DNA interacting molecule". These two terms do not have a well established meaning in the art and do not provide the skilled person with sufficient information to determine firstly the true scope of these claims, and secondly whether or not the claim is indeed differentiated

over the prior art (Preliminary Examination Guidelines III 4.5a). The true nature of the subject matter of these claims is such that it is vague, obscure and unclear according to Art. 6 PCT. The above applies equally to the compositions, synthesis and uses of these compounds specified in claims 17-29. Furthermore, the terms "incorporating molecules" used to further define the DNA interacting molecule in claim 13 is so unclear, and is further not elaborated in the description by means of any examples, that it is as unclear as the more generic term ("DNA interacting molecule") of which it is a preferred value. Exactly the same applies to the term "Synthetic steroids" as used in claim 12.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMGD		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CH99/00384	19/08/1999	21/08/1998
International Patent Classification (IPC) or national classification and IPC C07J43/00		
Applicant FREY, Felix et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 19 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/03/2000	15.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Watchorn, P Telephone No. +31 70 340 2207

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CH99/00384

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-68 as originally filed

Claims, No.:

1-29 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-13,17-29 (not examined in part) 14-16 (not examined at all).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-13,17-29 (not examined in part) 14-16 (not examined at all) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-13,17-29 (not examined in part) 14-16 (not examined at all).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-13,17-29 (not examined in part) 14-16 (not examined at all).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13,17-24,26-29
	No:	Claims	25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13,17-29
Industrial applicability (IA)	Yes:	Claims	1-13,17-22,25,27,29
	No:	Claims	23,24,26,28

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III - Non-Establishment of an Opinion

1) The compounds of claims 1-16 are defined in terms of a result to be achieved, i.e. in terms of being a conjugate between a "steroid hormone" and a "DNA interacting molecule". These two terms do not have a well established meaning in the art and do not provide the skilled person with sufficient information to determine firstly the true scope of these claims, and secondly whether or not the claim is indeed differentiated over the prior art. The true nature of the subject matter of these claims is such that it is so vague, obscure and unclear according to Art. 6 PCT that a meaningful search could not be carried out on these claims in full. Consequently the search was limited to those specific groups of "steroid hormones" and "DNA interacting molecules" that the applicant mentioned and sufficiently defined and exemplified in the application as provided for under Article 17(2)(a)(ii),(b) PCT. The above applies equally to the compositions, synthesis and uses of these compounds specified in claims 17-29. Furthermore, the terms "incorporating molecules" used to further define the DNA interacting molecule in claim 13 is so unclear, and is further not elaborated in the description by means of any examples, that it is as unclear as the more generic term ("DNA interacting molecule") of which it is a preferred value. Consequently this term was not taken into consideration in drafting the present non-unity since it is so obscure within the meaning of Art. 6 PCT and is consequently also excluded from any search under Art.17(2)(a)(ii)(b) PCT. Exactly the same applies to the term "Synthetic steroids" as used in claim 12.

2) Consequently the same subject matter of the present application as was excluded from the international search is now also excluded from examination according to Art.34(4)(a)(ii) PCT and for the same reasons (given above) of a lack of clarity that lead to the partial search. The examination is limited to that subject matter which was subject to an international search, additionally because the International Preliminary Examining Authority is under no obligation to examine unsearched subject matter (Rule 66.1(e) PCT).

Section IV - Lack of Unity of Invention

The most relevant prior art with regard to the unity of the present application consists of the following documents:-

D1 = WO-A-96/18372
D2 = WO-A-96/03875
D3 = WO-A-94/23751
D4 = WO-A-93/07283

The presently claimed subject matter relates to conjugates of steroid hormones with chemical groups which bind to nucleic acids (in particular DNA). The problem to be solved by the subject matter of this application (i.e. by these compounds) is the provision of agents capable of transfecting nucleic acids into the cell nucleus (see page 4, paragraph 1 of the description). It is this combination of the nuclear specificity conferred by the steroid hormone and the nucleic acid (NA) binding capability of the NA-interacting group present in the claimed compounds which is common to the claimed subject matter as a whole (which claims either the compounds per se, their uses compositions and syntheses) and which may serve to unify the claimed subject matter a priori.

In this regard it is noted that the above documents all disclose compounds which consist of conjugates of steroid hormones with chemical groups which interact with nucleic acids, see in particular:-

D1 - page 26, lines 1-21 and page 27 lines 8-18 and page 30, lines 6-10.

D2 - page 11, example 1

D3 - fig 1, page 34, example 1.10

D4 - page 46, paragraph 2 - page 47, paragraph 1

In the above mentioned passages document D1 discloses the conjugation of androsterone, other sex steroids and Vitamin D derivatives and corticoid steroids to a cationic group, D2 discloses the conjugation of dihydrotestosterone to a polylysine group, document D3 discloses the conjugation of estradiol to a polycationic peptide and document D3 discloses the general concept of conjugating an "internalisation factor" with a DNA binding agent, in particular, D4 mentions on page 46, paragraph 2- page 47, paragraph 1, the use of thyroid hormone (the applicant intends the term "steroid hormone" as used in claim 1 to include thyroid hormone - see claim 10) as the "internalisation factor" and, for example, polycations such as polylysine as the DNA binding agent (see page 49, paragraphs 2,3 of D4) or intercalating agents such as acridine or ethidium (see page 49, paragraph 4 - page 50 paragraph 1 of D4).

Furthermore, the steroid-DNA binding group conjugates of all of the above documents are directed to the solution of the same problem (delivery of nucleic acids to the cell nucleus) - see D1, page 21, paragraph 2, D2, page 12, paragraph 3, D3, page 4, paragraph 2 and D4 page 8, paragraph 2). Consequently documents D1-D4 represent the same technical solution to the same technical problem. Consequently the above mentioned feature, common to the claimed subject matter as a whole, has already been associated with the solution to the same problem in the prior art. Consequently this technical feature of the claimed subject matter cannot be considered to be the common or corresponding special technical feature within the meaning of Rule 13.2 PCT which differentiates the claimed subject matter as a whole over the prior art. Since according to Rule 13.2 PCT the presence of such a common or corresponding special technical feature is an absolute prerequisite for unity to be established, and given that there does not appear to be any other technical feature common to the claimed subject matter as a whole which might be able to fulfill this
role, the currently claimed subject matter lacks unity according to Rule 13.1

PCT.

Consequently the claimed subject matter was firstly broken up on the basis of the nature of the steroidal part of structure (subject to the restrictions made under Rule 66.1(e) PCT and Article 34(4)(a)(ii) PCT see Section III above). This division of the claimed subject matter establishes a further essential feature (which in the present case is the nature of the steroid group, estrogen, androgen... etc) which was originally presented in the claims as one of a number of alternatives, but is made an essential feature of each of the subjects of the present non unity, such that each of the subjects into which the presently claimed subject matter has been split, presents one further common technical feature (i.e. essential feature) which is a candidate to be a common or corresponding special technical feature. This division of the claimed subject matter results in 7 claimed inventions being conjugates of DNA interacting molecules with respectively:-

(1) corticoid hormones (embracing mineral and gluco-corticoids),

(2) androgens,

(3) estrogens,

(4) gestagens (progesterone agonists)

(5) * retinoids

(6) * thyroid hormones and

(7) * vitamin D derivatives

*(NOTE, according to the applicant's definition the term "steroid hormone" embraces retinoids, thyroid hormones and vitamin D compounds - see page 5, last paragraph).

However, as has already been shown above cited documents conjugates of NA interacting groups with various steroid hormones have already been disclosed as solutions to the same problem in the prior art, these hormones of the conjugates being specifically:-

(a) androgens (see D1, page 27, lines 8-18 where androsterone is conjugated to polyamine-NA interacting groups, see D2 page 11, and example 1, where dihydrotestosterone is conjugated to NA-interacting polylysine)

(b) estrogens (see D3, Fig 1, and page 34, example 1.10 where estradiol is conjugated to a cationic DNA interacting peptide)

(c) corticoid compounds (see D1, page 26, lines 1-21 where the conjugation of corticoid compounds to NA interacting polyamines is disclosed)

(d) Vitamin D derivatives (see D1, page 26, lines 1-21 where the conjugation of Vitamin D compounds to NA interacting polyamines is disclosed).

(e) sex hormones in general (see D1, page 26, lines 1-21 where sex hormones in general, which includes the well known class of progesterone agonists, including progesterone itself, which is also disclosed for this use in claim 3 of D3)

(f) thyroid hormones (see D4, page 46, paragraph 2 - page 47, paragraph 1)

Consequently the additional common technical feature of above subjects (1)-(4), (6) and (7), which may have unified these claimed inventions a priori, has also already been associated with the solution to the same technical problem in

the prior art. Consequently in the case of above identified subjects (1)-(4) (6) and (7), the nature of the "steroid hormone" part of the molecule cannot be considered to be the common or corresponding special technical feature within the meaning of Rule 13.2 PCT which distinguishes the subject matter of each of these claimed inventions as a whole over the prior art. Since no other technical feature could be identified in any of these subjects which might be able to fulfill this role, and further given that according to Rule 13.2 PCT the presence of such a special technical feature is an absolute prerequisite for unity to be established, these claimed inventions further lack unity within themselves according to Rule 13.1 PCT. Consequently yet another technical feature, originally presented in the application as originally filed as an alternative feature, is taken into
consideration in further dividing up the claimed subject matter of these claimed inventions. This feature is the nature of the NA-interacting group (intercalator, cross linking agent... etc).

Consequently each of claimed inventions (1)-(4) (6) and (7) as identified above, has been further split on the basis of the NA-interacting group (subject to the restrictions mentioned in section III above), such that it present yet another essential feature which acts as a further candidate for the special technical feature within the meaning of Rule 13.2 PCT.

With due regard to the decision T110/82 concerning the relationship between the interests of a rational procedure up to grant, in which interconnected matter should not needlessly be split up nor unrelated inventions lumped together for the purposes of saving fees, in particular since the expense for the procedure for such cases must be partly borne by the fees levied for other applications, the present application has been split up as follows, based on the different characterising features of these claimed inventions as set out below, and pursuant to Article 34(3)(a) PCT.

1. Claims: 1-13,17-29 (in part)
Conjugates of corticoids with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic

acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

2. Claims: 1-14, 17-29 (in part) 15,16 (in full)
Conjugates of corticoids with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

3. Claims: 1-13,17-29 (in part)
Conjugates of corticoids with DNA-ionic-interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

4. Claims: 1-9,12,13,17-29 (in part)
Conjugates of androgens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

5. Claims: 1-9,12-14,17-29 (in part)
Conjugates of androgens with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

6. Claims: 1-9,12,13,17-29 (in part)
Conjugates of androgens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

7. Claims: 1-9,12,13,17-29 (in part)

Conjugates of estrogens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

8. Claims: 1-9,12-14,17-29 (in part)
Conjugates of estrogens with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

9. Claims: 1-9,12,13,17-29 (in part)
Conjugates of estrogens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

10. Claims: 1-9,12,13,17-29 (in part)
Conjugates of gestagens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

11. Claims: 1-9,12-14,17-29 (in part)
Conjugates of gestagens with DNA-cross linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

12. Claims: 1-9,12,13,17-29 (in part)
Conjugates of gestagens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

13. Claims: 1-9,12-14,17-29 (in part)
Conjugates of retinoids with DNA-intercalating agents, cross linking agents or ionic interacting agents methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

14. Claims: 1-9,12,13,17-29 (in part)
Conjugates of Vitamin D compounds with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

15. Claims: 1-9,12-14,17-29 (in part)
Conjugates of Vitamin D compounds with DNA-cross linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

16. Claims: 1-9,12,13,17-29 (in part)
Conjugates of Vitamin D compounds with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

17. Claims: 1-9,12,13,17-29 (in part)
Conjugates of thyroid hormones with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

18. Claims: 1-9,12-14,17-29 (in part)
Conjugates of thyroid hormones with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with

nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

19. Claims: 1-9,12,13,17-29 (in part)
Conjugates of thyroid hormones with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

However, since the same finding of a lack of unity as made above was also raised at the stage of the international search (involving the division of the claimed invention into the same 19 different separate claimed inventions) and the applicant did not pay any additional search fees for any of the additional 18 claimed inventions according to Art.17(3)(a) PCT, Rule 40.2(a) PCT and the then valid Rule 104a(1) EPC (as of 01.03.2000 renumbered to Rule 105(1) EPC), only the main invention first mentioned in the claims (claimed invention 1 - see above) was subject to an international search according to Art.17(3)(a) PCT and no search was carried out in respect of any of claimed inventions 2-18. Consequently, since the EPO acting in its capacity as International Preliminary Examining Authority is not obliged to examine unsearched inventions (Rule 66.1(e) PCT) no invitation to pay additional examination fees has been sent according to Art.34(3)(a) PCT, Rule 68.2 PCT and Rule 105(2) EPC.

Section V - Assessment of Novelty, Inventive Step and Industrial Applicability

The following documents constitute the most relevant state of the art:-

D1 = WO-A-96/18372
D5 = Bioorg. Med. Chem. Lett. Vol 5(15) pp 1577-1580 (1995)

D6 = Chem. Abs. Vol 125:058,963

The following documents are also relevant for the assessment of the patentability of the claimed invention:-

D7 = Bioconjugate Chem. Vol 4(1) pp 85-93 (1993)
D8 = Bioconjugate Chem. Vol 2(4) pp 226-231 (1991)

Industrial Applicability (Art.34(4) PCT)

1) For the assessment of the present claims 23,24,26 and 28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty (Art.34(2) PCT)

1) The conjugates of glucocorticoids and DNA-intercalating agents of above identified claimed invention 1 and claimed per se in claims 1-13 differentiate themselves over the cation-corticoid conjugates of D1 - see page 26, lines 1-21 in that they the DNA-binding component of the conjugate is DNA-intercalating group whereas that of the conjugate of D1 is a cationic DNA-binding agent, which binds DNA by ionic interaction with the negatively charged phosphate backbone. The claimed conjugates are novel over the conjugates of documents D5 and D6 (D5 - see the figure on page 1578 and page 1577, paragraph 1; ,D6 - see the abstract), because the conjugates of these documents consist of glucocorticoids conjugated directly to nucleic acids, rather than being bound to nucleic acid by conjugation to a DNA-interacting group. Consequently the glucocorticoid-DNA-intercalating agent conjugates of claims 1-13 are novel according to Art.34(2) PCT. Since the processes of claims 17-19 are

characterised by the production of these glucocorticoid-DNA-intercalating agent conjugates, the subject matter of these claims (in far as they correspond to the production of compounds of claimed invention 1) are also novel according to Art.33(2) PCT. Furthermore, since the complexes of claim 20, the method for their production according to claims 21 and 22, the methods for the use thereof according to claims 23, 24 and 28, the pharmaceutical compositions of claim 27, and an assay for the effectiveness thereof according to claim 29 are all characterised by the use/presence/production of compounds according to claim 1, then these claims are also novel according to Art.33(2) in as far as they relate to uses/methods/complexes/assays characterised by the use/presence/production of glucocorticoid-DNA-intercalating agent conjugates according to claimed invention 1.

2) However, claim 25 relates to a cell transfected with a complex according to claim 20 (consisting of a nucleic acid and a compound according to claim 1). In this regard it is not evident that the use of this particular transfection agent would result in a transformed cell any different from a transformed cell produced by using the same gene transfected by means of a different transfection agent. For example, the transfection experiments disclosed in documents D2 (see example 3), D7 (see page 88, column 2, paragraph 4 - page 89, column 1, paragraph 1), D8 (see page 228, column 1, paragraph 2 - page 229, column 1, paragraph 2) also result in transformed cells containing a newly introduced gene, albeit by means of a different transfection agent to that used to create the cells of claim 25. However, there is no indication in the application nor any technical reason to suppose that the use of the claimed transfection agents (of claimed invention 1) would result in a cell different from one transfected with the same gene, but using a different transfection agent - a product is not necessarily rendered novel by virtue of being produced by a novel process and there is no reason to assume that the use of a different transfection agent would somehow alter the cell produced (improved efficiency of transfection does not mean that the cell is different) - see Preliminary Examination Guidelines IV 7.5. Furthermore, it cannot be argued that the nuclear specificity conveyed on the complex by the presence of the Glucocorticoid in the conjugate could result in a cell transfected in a such a way as to be different over the transfected cells of

the state of the art, because the transfection experiment performed in document D2 made use of steroid-polylysine conjugate which also had nuclear specificity (see page 12, paragraph 3 of D2). Consequently claim 25 lacks novelty over, amongst others, documents D2, D7 and D8 according to Art.33(2) PCT (it would be impossible to cite all documents relating to transfected cells, all of which could potentially prejudice the novelty of claim 25, so the cited documents used in this objection have been limited to those relating to the use of conjugates containing steroid or intercalating groups).

3) The method of claim 26 discloses the use of the transfected cells of claim 25 for the treatment of a human being, whereas documents D1-D4 all disclose the use of the transfection complexes directly in treatment (without first transfecting a cell line and then using this in the treatment). Claim 26 is consequently novel over the above cited prior art according to Art.33(2) PCT.

Inventive Step - Art.33(3) PCT

1) The presently claimed subject matter of claimed invention 1 relates to compounds which are conjugates of corticosteroid hormones with chemical groups which intercalate with nucleic acids (in particular DNA). The problem to be solved by the subject matter of this claimed invention (i.e. by these compounds) is the provision of agents capable of transfecting nucleic acids into the cell nucleus (see page 4, paragraph 1 of the description). The presence of the corticosteroid hormone in the transfection conjugates of claimed invention 1 as claimed per se in claims 1-13 confers nuclear specificity on the transfection conjugate and facilitates delivery of the nucleic acid (bound to the intercalating agent part of the conjugate) to the nucleus of the target cell. In this regard it is noted that document D1 clearly indicates the use of corticosteroid hormones attached to nucleic acid binding cationic groups (see page 26, lines 1-21 of D1), where the presence of the corticosteroid hormone confers nuclear specificity on the conjugate and the nucleic acid with which it is complexed (see page 21, paragraph 2 of D1). Furthermore, it is noted that the conjugation of the known glucocorticoid compound - dexamethasone, via a linker group directly to nucleic acids confers nuclear specificity on the nucleic acid (see D5, the figure on page

1578 and page 1577, paragraph 1), D6 indicates the same to be true for the conjugation of deoxycorticosterone to nucleic acids. Furthermore, it is also noted that documents D7 and D8 clearly disclose the use of intercalating agents as a nucleic acid binding group, conjugated to agents which confer some kind of specificity on the DNA linked to the intercalator component of the conjugate - in D7 this is a conjugate of acridine (intercalator) linked to a cell specific glycoside (see page 86, Figure 1 of D8) which was used successfully in transfection experiments (see page 88, column 2, paragraph 4 - page 89, column 1, paragraph 1 of D7) - in D8 this was ethidium (intercalator) conjugated to transferrin (see page 227, column 2, paragraph 2 - page 228, column 1, paragraph 1 of D8), where the transferrin component of the conjugate facilitated transferring receptor mediated endocytosis of the [transferrin-ethidium]:DNA complex into the target cell. The skilled person, when confronted by the above mentioned problem, would transfer the above teaching of documents D7 and D8 (that the DNA- binding group of a [DNA-binding-group]-[specificity-conferring-group] - transfection agent, can be a nucleic acid intercalating agent such as acridine or ethidium) over to the above mentioned teaching of D1, D5 and D6 (that the presence of a glucocorticoid as the specificity conferring group in such a [DNA-binding-group]-[specificity-conferring- group] - transfection agent confers nuclear specificity of nucleic acid delivery). This obvious step results in the [glucocorticoid]-[intercalating agent] conjugates of claimed invention 1 as claimed per se in claims 1-13, consequently these compounds are an obvious solution to the above mentioned problem and as such lack inventive step according to Article 33(3) PCT, since the uses/processes/methods/complexes of claims 17-29 do not appear to possess and further technical features which might render these claims inventive in their own right, they also lack inventive step according to Article 33(3) PCT.

Section VII

1) The applicant has not ackowledged documents D1-D3 as the closest state of the art in the description as required by Rule 5.1(a)(ii) PCT.

S ction VIII

1) The compounds of claims 1-13 are defined in terms of a result to be achieved, i.e. in terms of being a conjugate between a "steroid hormone" and a "DNA interacting molecule". These two terms do not have a well established meaning in the art and do not provide the skilled person with sufficient information to determine firstly the true scope of these claims, and secondly whether or not the claim is indeed differentiated over the prior art (Preliminary Examination Guidelines III 4.5a). The true nature of the subject matter of these claims is such that it is vague, obscure and unclear according to Art. 6 PCT. The above applies equally to the compositions, synthesis and uses of these compounds specified in claims 17-29. Furthermore, the terms "incorporating molecules" used to further define the DNA interacting molecule in claim 13 is so unclear, and is further not elaborated in the description by means of any examples, that it is as unclear as the more generic term ("DNA interacting molecule") of which it is a preferred value. Exactly the same applies to the term "Synthetic steroids" as used in claim 12.

INTERNATIONAL SEARCH REPORT

Int. ional application No.
PCT/CH 99/00384

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 23,24,26 and 28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-27 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

"see further info"

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13, 17-29 (partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-27 (in part)

The compounds of claims 1-16 are defined in terms of a result to be achieved, i.e. in terms of being a conjugate between a "steroid hormone" and a "DNA interacting molecule". These two terms do not have a well established meaning in the art and do not provide the skilled person with suffificient information to determine firstly the true scope of these claims, and secondly whether or not the claim is indeed differentiated over the prior art. The true nature of the subject matter of these claims is such that it is so vague, obscure and unclear according to Art. 6 PCT that a meaningful search cannot be carried out on these claims in full. Consequently the search has been limited to those specific groups of "steroid hormones" and "DNA interacting molecules" that the applicant has mentioned and sufficiently defined and exemplified in the application as provided for under Article 17(2)(a)(ii),(b) PCT. The above applies equally to the compositions, synthesis and uses of these compounds specified in claims 17-29. Furthermore, the terms "incorporating molecules" used to further define the DNA interacting molecule in claim 13 is so unclear, and is further not elaborated in the description by means of any examples, that it is as unclear as the more generic term ("DNA interacting molecule") of which it is a preferred value. Consequently this term was not taken into consideration in drafting the present non-unity since it is so obscure within the meaning of Art. 6 PCT and is consequently also excluded from any search under Art.17(2)(a)(ii)(b) PCT. Exactly the same applies to the term "Synthetic steroids" as used in claim 12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...mation on patent family members

...al Application No
PCT/CH 99/00384

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9618372 A	20-06-1996	US 5650096 A	22-07-1997
		US 5747471 A	05-05-1998
		AU 4516196 A	03-07-1996
		CA 2205968 A	20-06-1996
		EP 0799059 A	08-10-1997
		JP 10510813 T	20-10-1998
		US 5767099 A	16-06-1998
		US 5840710 A	24-11-1998
		US 5719131 A	17-02-1998
		US 5910487 A	08-06-1999
		US 5783565 A	21-07-1998
		US 5948767 A	07-09-1999
		US 5939401 A	17-08-1999
WO 9603875 A	15-02-1996	AU 3071995 A	04-03-1996
		CA 2197770 A	15-02-1996
		EP 0773719 A	21-05-1997
WO 9423751 A	27-10-1994	AU 6568594 A	08-11-1994
		DE 4412629 A	26-01-1995
		EP 0693939 A	31-01-1996
US 5614503 A	25-03-1997	NONE	
WO 9307283 A	15-04-1993	AU 671084 B	15-08-1996
		AU 2652692 A	03-05-1993
		BG 98718 A	28-02-1995
		BR 9206559 A	08-11-1994
		CA 2118816 A	31-03-1993
		CZ 9400746 A	17-05-1995
		EP 0545016 A	09-06-1993
		EP 0607206 A	27-07-1994
		FI 941474 A	30-03-1994
		HU 71312 A	28-11-1995
		HU 9500694 A	29-01-1996
		JP 10506001 T	16-06-1998
		MX 9205543 A	01-05-1993
		NO 941154 A	29-03-1994
		NZ 244306 A	26-07-1995
		SG 44680 A	19-12-1997
		SK 36894 A	10-08-1994
		US 5981273 A	09-11-1999
		US 5547932 A	20-08-1996
		ZA 9207460 A	21-02-1994
		CN 1070946 A	14-04-1993

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SMGD		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CH 99/00384	19/08/1999	21/08/1998
Applicant		
FREY, Felix et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

CONGUGARES OF DNA INTERACTING GROUPS WITH STEROID HORMONES FOR USE AS NUCLEIC ACID TRANSFECTION AGENTS

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. -

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATI L SEARCH REPORT

International application No.
PCT/CH 99/00384

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 23,24,26 and 28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-27 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

"see further info"

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13, 17-29 (partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-27 (in part)

The compounds of claims 1-16 are defined in terms of a result to be achieved, i.e. in terms of being a conjugate between a "steroid hormone" and a "DNA interacting molecule". These two terms do not have a well established meaning in the art and do not provide the skilled person with suffificient information to determine firstly the true scope of these claims, and secondly whether or not the claim is indeed differentiated over the prior art. The true nature of the subject matter of these claims is such that it is so vague, obscure and unclear according to Art. 6 PCT that a meaningful search cannot be carried out on these claims in full. Consequently the search has been limited to those specific groups of "steroid hormones" and "DNA interacting molecules" that the applicant has mentioned and sufficiently defined and exemplified in the application as provided for under Article 17(2)(a)(ii),(b) PCT. The above applies equally to the compositions, synthesis and uses of these compounds specified in claims 17-29. Furthermore, the terms "incorporating molecules" used to further define the DNA interacting molecule in claim 13 is so unclear, and is further not elaborated in the description by means of any examples, that it is as unclear as the more generic term ("DNA interacting molecule") of which it is a preferred value. Consequently this term was not taken into consideration in drafting the present non-unity since it is so obscure within the meaning of Art. 6 PCT and is consequently also excluded from any search under Art.17(2)(a)(ii)(b) PCT. Exactly the same applies to the term "Synthetic steroids" as used in claim 12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-13,17-29 (in part)

Conjugates of corticoids with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

2. Claims: 1-14, 17-29 (in part) 15,16 (in full)

Conjugates of corticoids with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

3. Claims: 1-13,17-29 (in part)

Conjugates of corticoids with DNA-ionic-interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

4. Claims: 1-9,12,13,17-29 (in part)

Conjugates of androgens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

5. Claims: 1-9,12-14,17-29 (in part)

Conjugates of androgens with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

6. Claims: 1-9,12,13,17-29 (in part)

Conjugates of androgens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

7. Claims: 1-9,12,13,17-29 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates of estrogens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

8. Claims: 1-9,12-14,17-29 (in part)

Conjugates of estrogens with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

9. Claims: 1-9,12,13,17-29 (in part)

Conjugates of estrogens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

10. Claims: 1-9,12,13,17-29 (in part)

Conjugates of gestagens with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

11. Claims: 1-9,12-14,17-29 (in part)

Conjugates of gestagens with DNA-cross linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

12. Claims: 1-9,12,13,17-29 (in part)

Conjugates of gestagens with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

13. Claims: 1-9,12-14,17-29 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates of retinoids with DNA-intercalating agents, cross linking agents or ionic interacting agents methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

14. Claims: 1-9,12,13,17-29 (in part)

Conjugates of Vitamin D compounds with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

15. Claims: 1-9,12-14,17-29 (in part)

Conjugates of Vitamin D compounds with DNA-cross linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

16. Claims: 1-9,12,13,17-29 (in part)

Conjugates of Vitamin D compounds with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

17. Claims: 1-9,12,13,17-29 (in part)

Conjugates of thyroid hormones with DNA-intercalating agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

18. Claims: 1-9,12-14,17-29 (in part)

Conjugates of thyroid hormones with DNA-cross-linking agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

19. Claims: 1-9,12,13,17-29 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates of thyroid hormones with DNA-ionic interacting agents, methods for their production, pharmaceutical compositions thereof, complexes thereof with nucleic acid and their use in cell transfection, cells transfected therewith and assays for that transfection.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 99/00384

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J43/00 C07J41/00 C12N15/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. HAENSLER ET AL: "Synthesis and Characterization of a Trigalactoysylated Bisacridine Compound To Target DNA to Hepatocytes" BIOCONJUGATE CHEMISTRY., vol. 4, no. 1, January 1993 (1993-01) - February 1993 (1993-02), pages 85-93, XP002092510 WASHINGTON US page 86; figure 1 page 88, column 2, paragraph 4 -page 89, column 1, paragraph 2 --- -/--	1-12, 15-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 1999	18. 01. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	WATCHORN P.W.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WAGNER E ET AL: "DNA-BINDING TRANSFERRIN CONJUGATES AS FUNCTIONAL GENE-DELIVERY AGENTS: SYNTHESIS BY LINKAGE OF POLYLYSINE OR ETHIDIUM HOMODIMER TO THE TRANSFERRIN CARBOHYDRATE MOIETY" BIOCONJUGATE CHEMISTRY, vol. 2, no. 4, 1 July 1991 (1991-07-01), pages 226-231, XP000327278 page 227, column 2, paragraph 2 -page 229, column 1, paragraph 2; figure 1 ---	1-12, 15-27
Y	CHEMICAL ABSTRACTS, vol. 125, no. 5, 29 July 1996 (1996-07-29) Columbus, Ohio, US; abstract no. 58963, N. CHIDAMBARAM ET AL: "Targeting of Antisense: Synthesis of Steroid Linked and Steroid Bridged Oligodeoxyribonucleotides" page 1206; column 1; XP002092511 abstract & DRUG DELIVERY, vol. 3, no. 1, 1996, pages 27-33, ---	1-12, 15-27
Y	ACEDO M ET AL: "Preparation of Oligonucleotide-Dexamethasone conjugates" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 15, 3 August 1995 (1995-08-03), page 1577-1580 XP004135387 see the steroid conjugate on page 1578 page 1577, paragraph 1 ---	1-12, 15-27
Y	WO 96 18372 A (GENZYME CORP) 20 June 1996 (1996-06-20) page 26, line 1 - line 21 page 27, line 8 - line 18 page 30, line 6 - line 10 page 21, paragraph 2 ---	1-12, 15-27
Y	WO 96 03875 A (UNIV EMORY) 15 February 1996 (1996-02-15) page 11; examples 1-3 page 12, paragraph 3 ---	1-12, 15-27
Y	WO 94 23751 A (BOEHRINGER MANNHEIM GMBH ;SUROVOY ANDREJ (DE); DANNULL JENS (DE);) 27 October 1994 (1994-10-27) page 4, paragraph 2 page 34; claim 3; figure 1; example 1.10 ---	1-12, 15-27
Y	US 5 614 503 A (BODEPUDI VEERAIAH ET AL) 25 March 1997 (1997-03-25) column 2, line 12 - line 23 ---	1-12, 15-27

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 99/00384

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 07283 A (BOEHRINGER INGELHEIM INT ;UNIV NORTH CAROLINA (US); GENENTECH INC) 15 April 1993 (1993-04-15) the whole document	1-12, 15-27

Form PCT/ISA/210 (continuation of second sheet) (July 1992)